

Pioneer Innovator Grant 2-2022

Project title: Somatostatin receptor 4 selective cone snail peptides as drug leads for non-opioid pain relief

Application number: 0079350

Applicant name: Walden Bjørn-Yoshimoto

Main Applicant position: Assistant Professor

Administrating institution: Faculty of Health and Medical Sciences - University of Copenhagen

Co-applicants:

Grant period in years:	1
Total requested budget:	kr 1.000.000
Received from administrating institution:	0
Received from other sources:	0
Applied from other sources:	0

Applicant

Main Applicant Personal Information

Full name:	Walden Bjørn-Yoshimoto	E-mail address:	waldenb@gmail.com
Phone number:		Gender:	Male
Nationality:	Danish	Date of birth:	1983-06-27
Country of residence:	Denmark	ORCID:	0000-0003-1019-9239
Months of approved leave following PhD degree date:	3		

Institution

Administering Institution

Administering Institution:	Faculty of Health and Medical Sciences - University of Copenhagen
Department / Institute:	Department of Biomedical Sciences
Division:	
Phone no:	3532 7428
City:	Copenhagen N
Country:	Denmark

Proposal

Project Information

Project title

Somatostatin receptor 4 selective cone snail peptides as drug leads for non-opioid pain relief

Brief project description

Current pain medications include opioids, antipsychotics, anticonvulsants, and anti-inflammatory drugs. Each of these have major drawbacks, including addiction, side effects, drug interactions, 'desensitization' (decreased effect over time), and low efficacy. Currently, the most efficacious pain medication available is arguably opioids which are highly addictive and carry a high risk of respiratory depression. Thus, although the use of opioids is largely being discouraged, health professionals and patients are left with little choice.

We have identified a potent and selective agonist of the somatostatin receptor

(SST) 4, a novel molecular target for pain relief. Our compound shows efficacious pain relief in animal models of post-surgical pain and neuropathic pain. Based on the molecular target of this compound, we also anticipate it to be effective for treating inflammatory pain. Experiments to address this are currently underway. We are applying for this grant to further **develop our compound as a novel non-opioid pain medication.**

In the 7 major markets (7MM) alone, an estimated **187 million people suffer from chronic pain**, many of which are still using opioids.

We are well underway developing this range of SST4 agonist and additional analogs, and in the proposed project we aim to continue this work in a way that will significantly de-risk the asset and make a future spin-out an attractive investment opportunity. Specifically, this proposal will encompass **the following activities:**

- Physiochemical, stability, permeability, and plasma binding studies on 5-6 front runners.
- Pharmacokinetic studies on the drug lead selected from the above.
- File national phase applications for the IP in important territories.
- Secure legal consulting on licensing deals.

Project description

Background and Purpose

The problem

While about 1 in 5 people suffer from various chronic pain indications, current pharmacological interventions are ill-suited to treat the majority of these. The most effective pain medications are opioids. They are of course addictive, and lead to immense personal and societal issues, but are also less effective for chronic treatment due to their tendency to “desensitize”, thereby decreasing efficaciousness over time¹. Alternatives exist but have problems of their own². No n-steroid anti-inflammatory drugs are used for some pain indications, including cancer-related pain, surgical pain, and various mild pain indications. However, these drugs have a sleuth of adverse effects and contraindications due to harmful drug interactions, including serious cardiovascular risks. Anticonvulsants including gabapentin and pregabalin are used, especially for chronic neuropathic pain, though side effects such as respiratory issues, increased risk of suicide, and substance intoxication are common. Further, these drugs typically elicit withdrawal symptoms, suggesting physical substance dependence. Antipsychotics are also used for some pain indications, and while the second-generation antipsychotics do have a lower tendency to induce extrapyramidal side effects, they do still occur, as do numerous other side effects such as weight gain,

hypertriglyceridemia, and hyperglycemia³. Further, few randomized controlled studies have yet been performed to assess the effect of new antipsychotics on pain^{4,5}. Because of these drawbacks, opioids still retain a prominent role in pain management, causing immense societal and economic problems.

The opioid problem is certainly greatest in the USA, but it is increasingly spreading across the world. Even in Denmark, the rate of extraclinical opioid use is rapidly rising, as is the prescription rates of the more addictive varieties of opioids, such as oxycodone. In the USA, there were almost 1 million opioid-related hospitalizations in 2016. In 2019, an estimated 9.7 million Americans misused prescription opioids, and tens of thousands of Americans die each year from opioid overdoses⁶. Thus, the prevalence of debilitating opioids remains a curse for many people, both those personally affected by addiction, but also spreading repercussions into the wider society. While total cost of the opioid crisis costs can be difficult to assess, the American Addiction Centers calculated \$2.5 trillion from 2015 – 2018 just in the USA.

A solution

Somatostatin is a neuropeptide and peptide hormone that has wide-ranging physiological roles. These include the regulation of various other hormones such as growth hormone, insulin, glucagon, gastrin, cholecystokinin, and vascular endothelial growth factor, but also regulation of various catecholamines and stomach acid secretion⁷. While most often described as an inhibitory regulator of hormones, the somatostatin system is also involved in pain, most likely through the dorsal root ganglion (DRG) where somatostatin release from capsaicin-sensitive neurons was found to inhibit pain signaling^{8,9}. There are five somatostatin receptor (SST) subtypes in humans, and subtypes 1-4 are expressed in the DRG. The SST4 is of particular interest, since activation of this subtype is not expected to elicit the endocrine side effect associated with SST2, -3, or -5, or the growth hormone-, prolactin- and calcitonin-related side effects expected for SST1^{10,11}. The presence of the SST4 in the DRG therefore poses an interesting opportunity for a novel pain relief target (see Figure 1), though selective SST4 drugs have been difficult to produce. An SST1 and -4 selective peptide (TT-232), originally investigated for cancer treatment, was shown to alleviate pain, and more recently the same was shown for small molecule SST4 agonists^{12,13}.

Our solution

We have identified a small, modified peptide (HSH-109) that is a selective agonist at the SST4 and shows efficacious pain relief in several pain models. The peptide was first identified from the transcriptomes of cone snails, a group of marine predators that utilize a complex mix of peptide toxins, 'conotoxins', to incapacitate their prey. HSH-109 was discovered during the follow-up to our recently published

work which identified the first somatostatin agonist from cone snail venom, Ro1¹⁴. Ro1 was selective for the SST1, and -4, though with low micromolar potency, and when screened at 318 human G protein-coupled receptors (GPCRs), only these two receptors showed activation. Importantly, none of the opioid receptors showed activation. Ro1 was further determined to be extremely stable in plasma. Interestingly, Ro1 and related were almost identical to octreotide, a somatostatin drug analog developed in the 1970s to circumvent the instability of somatostatin itself¹⁵. This includes the shortening of a characteristic disulfide loop, as well as the introduction of a D-amino acid in the same position in the conotoxins and the drug analog. The fact that cone snails have engineered a drug so similar to the best human efforts is fascinating, though perhaps not surprising. These toxins require many of the same characteristics as drugs to elicit their function. Ro1 showed a robust pain relief effect in two mouse models, one for post-surgical pain, and one for acute thermal pain. In fact, Ro1 was as efficacious, but elicited a longer lasting pain relief than morphine. HSH-109 was subsequently identified from a large transcriptome database, and when synthesized, proved more potent and selective at the SST4. Further, we have developed numerous analogs, some with even better *in vitro* profiles (Figure 2). HSH-109 has been tested in two pain models, one of post-surgical pain, and one of neuropathic pain, where it was very efficacious (Figure 3).

Ongoing activities (concluded prior to Pioneer Innovator project start)

We are currently in the process of designing a new range of analogs based on the first set, as well as the recently published SST4 structure¹⁶. This round will, in addition to the SST activation, focus on improved “drug-like” properties, such as predicted solubility, logD, and stability. We will characterize these analogs *in vitro* and include several additional receptors of interest to rule out certain off-target effects. This includes the opioid receptors, as well as receptors closely related to the SSTs, e.g., the urotensin, ghrelin, and Mas-related receptors. On the *in vivo* side, we will find the dose range, and we will test HSH-109 and 1-2 analogs in a model of inflammatory pain, the complete Freund's adjuvant (CFA) model¹⁷, which is indicative of several pain indications with large groups of patients such as osteoarthritis and joint pain, a type of musculoskeletal pain disorder (MSPD)^{18,19}. These results will be ready prior to starting the proposed Pioneer Innovator project. Further, a priority patent application has been filed for the IP (HSH-109 and relevant analogs), and we are taking efforts during the remainder of the priority year to strengthen the patent claims.

Methods and design

The project

By the beginning of the proposed project, we will have selected 5-6 front runner candidates. We will have determined the *in vitro* profiles of all, and the *in vivo* data

of 1-2 representatives, ensuring that the *in vivo* potency correlates with the *in vitro* potency at the SST4. The current proposal will serve to further de-risk the project by identifying the lead compound, as well as advance the IP efforts by funding important national phase applications. We propose to de-risk by subjecting the 5-6 candidates to assays (work package 1) to determine:

- Solubility
- LogD determination at pH7.4 and pH4.0 (as our peptide structure and analog *in vitro* potency suggests that oral delivery could be feasible)
- Chemical stability at pH range (4-11)
- Caco-2 permeability
- Plasma stability (mouse and human)
- Plasma protein binding (mouse and human)
- Stability in microsomes

From the results from work package 1, we will select one lead, and continue with (work package 2):

- Initial pharmacokinetic studies
- Brain and spinal cord penetration
- Cytochrome P450 enzyme inhibition
- human Ether-à-go-go-Related Gene (hERG) screen
- Mini Ames

Funding applied for in this project will also be used to initiate national phase filing in the USA, EU, Canada, and Japan. This will be very advantageous for the future licensing of intellectual property (IP) from The University of Copenhagen (UCPH), as they typically require a broad geographic protection, as well as for future sublicensing deals or sales.

Lastly, a small amount of funding will be used for legal consulting on a licensing agreement between UCPH and our future spin-out company, potentially finalizing the agreement within the project timeline.

The feasibility

The current project proposal relies exclusively on contract research organizations (CROs) for two reasons. (1) the activities described are not our main competencies, these can be done better, faster, and cheaper by outsourcing, and (2) we will be focusing on other efforts in-house. This includes an upcoming research project that will characterize numerous additional conotoxins with activity at a range of GPCRs. Given the enormous impact of past conotoxin discoveries²⁰, we expect several of those to be of commercial interest. These would then feed into our future company's pipeline, avoiding the stigma (to investors) of being a

long-term “single asset” company.

Work package 1 will be performed by either ‘Bienta’ or ‘WuXi AppTech’, while work package 2 will be performed by WuXi AppTech. Both CROs are experts with decades of experience in delivering these services, and well-defined turnover times. The national phase filings will be handled by the patent law firm ‘Plougmann Vingtoft’, who has also filed the priority patent application. Consulting and potential negotiation of licensing deals will be undertaken by either ‘Lundgrens’ or ‘Life Science Plus’ law firms.

Assessment

The results

When this project is completed, we will have an extremely attractive asset. Specifically, we will have obtained the following:

- **Milestone 1** – Data from work package 1
 - This will give us an advanced understanding of the physiochemical properties and allow up to select our drug-lead.
- **Milestone 2** - Data from work package 2
 - This will give us an initial understanding of the ADME properties
- **Milestone 3** – National IP protection filed in important territories.

Combined, this will put us in a very good position to attract venture capital funding. It will also significantly increase the value of the IP and thereby increase the amount of investment we can obtain and/or decrease the share dilution by said investment. Further, we will either have, or be in a good position to achieve a favorable licensing agreement with the UCPH.

Commercial potential

Potential market

There is a strong inclination among physicians and national health agencies to replace opioids, though current alternatives are also often problematic. With more than 1 in 5 people suffering from chronic pain indications, the potential market is vast. Some of the largest chronic pain indications include chronic lower back pain, affecting 76.4 million people in the 7 major markets (7MM)²¹, various types of MSPDs (40 % of the population will experience musculoskeletal lower back pain during their life²²), inflammatory pain indications (osteoarthritis alone affects ~32.5 million just in the USA²³), and neuropathic pain (affecting 7-10% of the population²⁴). Many of these patients are either insufficiently treated, treated with opioids, or both. In fact, despite opioids being largely discouraged for use in MSPDs, a 2020 study reported that 21.5% of MSPD patients were prescribed opioid due to the lack of efficacious alternatives²⁵. With the number of people suffering from these conditions, it is not surprising that the market in the 7MM alone for pain

medication is in the billions of dollars. The 7MM market for MSPDs is estimated to be \$ 3.6 billion, and for chronic lower back pain this is an estimated \$ 7.2 billion. In the US, 1 in 5 chronic lower back pain patients are prescribed opioids, with three quarters of them reporting long-term use (more than a year)²⁶. Approximately 20-30% of patients receiving long-term opioid treatment develop an opioid use disorder²⁷. The increased awareness of this fuels an increased desperation for new alternatives.

The competition

Due in part to the societal problems, and in part the mammoth market size, there are numerous efforts focusing on development of non-opioid pain relief therapies. They range immensely in strategy and targets, with prominent examples largely focusing on the prostaglandin, endocannabinoid, serotonin, acetylcholine, and adenosine systems, or Na⁺ and Ca²⁺ channels, though a sizable part of the current pain medication pipeline (~11%) is still related to opioids²⁸. A few examples also exist of SST4 agonists. Clexio has a candidate, CLE-400, with some SST4 activity, though they emphasize its $\alpha 2$ adrenergic effect for dermal application²⁹. Perhaps more pertinent, an Eli Lilly small molecule SST4 agonist, LY3556050, recently completed phase II for osteoarthritis and chronic lower back pain³⁰. While this certainly validates the SST4 as a target to some degree, this could result in competition. Where HSH-109 differs, is that we have the first SST4-selective peptide drug. The main advantages are that we likely have:

- Better selectivity than small molecules.
- No toxic metabolites.
- No dangerous pharmacokinetic drug interactions.

The first point decreases the risk of off-target effects. The last two points are due to peptides' typically not being metabolized by the P450 system. Initial direct assessment of this will happen in work package 1 (microsome stability). A large proportion of chronic pain patients suffer from comorbidities, somewhat explained by the geriatric nature of this group³¹⁻³³. As such, drug interactions are of particular concern, and a significant portion of patients could thus be ineligible to use LY3556050. Further, given the size, predicted physiochemical properties, and *in vitro* potency of select analogs (Figure 2), we expect oral delivery of our candidate to be feasible. Initial indication of this will come from the Caco-2 permeability assays performed in work package 1. This circumvents arguably the most severe potential drawback of peptide drugs for this application. One other concern is of course production price, as this is typically substantially higher for peptides. However, for the size and minimal complexity of the candidate in question this is not expected to be prohibitive.

Research team

Aside from the data and IP assets, we are building a strong team to assist with taking this IP towards commercialization. Currently, this is composed of:

- Inventor, future founder/CSO/interim CEO: Assis Prof. Walden Bjørn-Yoshimoto (myself).
- Inventor, scientific advisor: Assoc Prof. Helena Safavi, an expert on the underlying technology with experience previously creating a spinout.
- Preclinical advisor: Sara Hestehave, an expert on preclinical pain models from both academia and the pharmaceutical industry.

We also have an ongoing collaboration with Assoc Prof. Kenneth Lindegaard Madsen, who has been performing some of the *in vivo* assays, and advising from his recent experience creating a spinout in Denmark. Further, I am in dialog with Prof. Lars Arendt-Nielsen, one of the leading Danish experts on clinical pain research and director of R&D in a CRO focusing exclusively on clinical development of interventions for pain and inflammation, who has expressed interest in collaborating on this venture.

I am currently sparring considerably with UCPHs internal business development consultants at 'Open Entrepreneurs' and have been encouraged by the involved parties to apply to join 'SPARK', the Stanford University-developed (Novo Nordisk Foundation-funded) mentoring program to improve translation and commercialization of academic research. To further refine my business development skills, I was admitted to the 'Entrepreneurship in Healthcare' course (by the Novo Nordisk Foundation-funded School of Health Innovation), which will start in September 2022. While these efforts will give me tools to start working on the business development more effectively, this would still be an interim role for me. Medium-term, we will employ additional business development consultation to assist, and long-term we will hire a dedicated business developer to fulfill this need.

Figures

Figure 1 – Mechanism of Action

The proposed mechanism of action for somatostatin-mediated pain relief by our compound. Somatostatin receptor 4 in the dorsal root ganglion is activated by our compound, thereby dampening subsequent signaling.

Figure 2 – Selected analogs

The first round of optimization produced 18 analogs with varying potencies and selectivity. The activity in the PRESTO-Tango assay at the five somatostatin receptors is shown in this heatmap for the seven most promising of these.

Somatostatin-14 (SRIF-14) and our first compound, HSH-109, are shown at the top. The values are pEC50 values and a white box with an “X” means that the curves did not complete at the highest tested concentration (300 µM).

Figure 3 – HSH-109 in mouse pain models

*The result of HSH-109 in two mouse pain models. (A) a model of post-surgical pain tested against a normal saline negative control and a morphine positive control. (B) a model of inflammatory pain, the spared nerve injury model, tested against a normal saline negative control and a gabapentin positive control. The full lines represent the ipsilateral side (the injured side, Ipsi) and the dashed lines represent the contralateral (control, Contra) side of the mouse. The left panels show the effect over time, while the right panel is an integration (area under the curve, AUC) of the data in the left panel. Data was analyzed using a Kruskal-Wallis test (A) or 2-way ANOVA with a Tukey post-test (B), and * = $p < 0.05$, ** = $p < 0.01$, **** = $p < 0.0001$.*

Abbreviation list

CFA: Complete Freund's Adjuvant

CRO: Contract Research Organizations

DRG: Dorsal Root Ganglion

GPCR: G protein-coupled receptor

hERG: human Ether-à-go-go-Related Gene

IP: Intellectual property

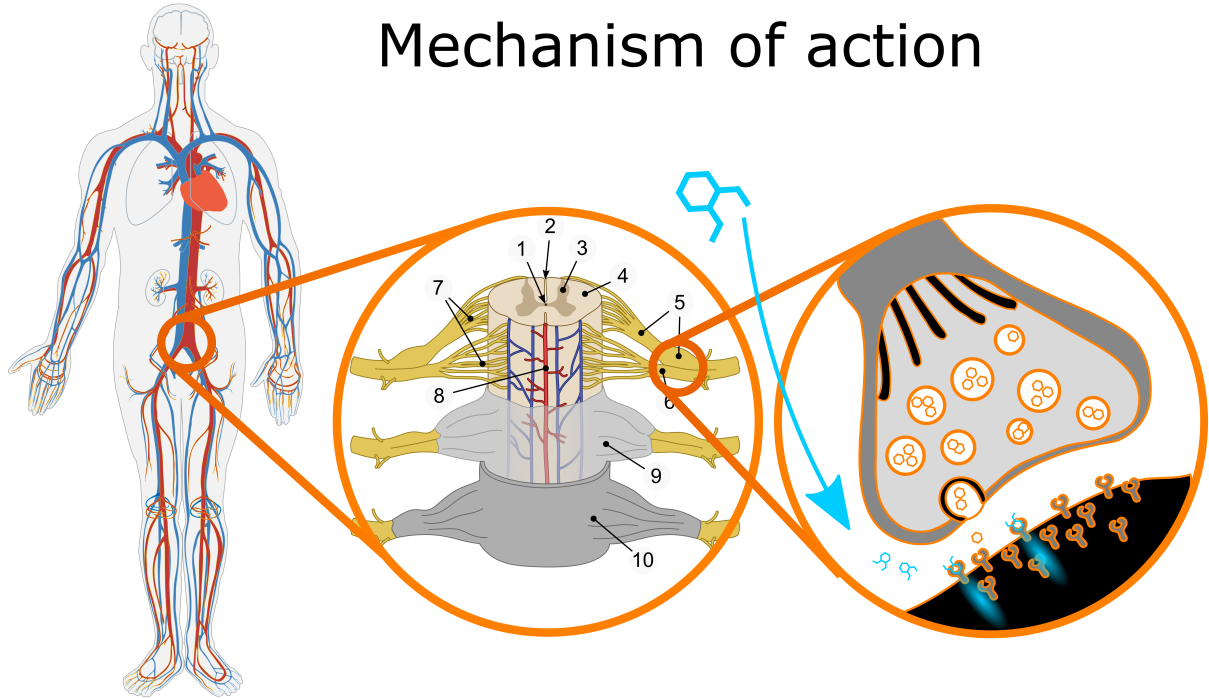
MSPD: Musculoskeletal Pain Disorders

SST: Somatostatin Receptor

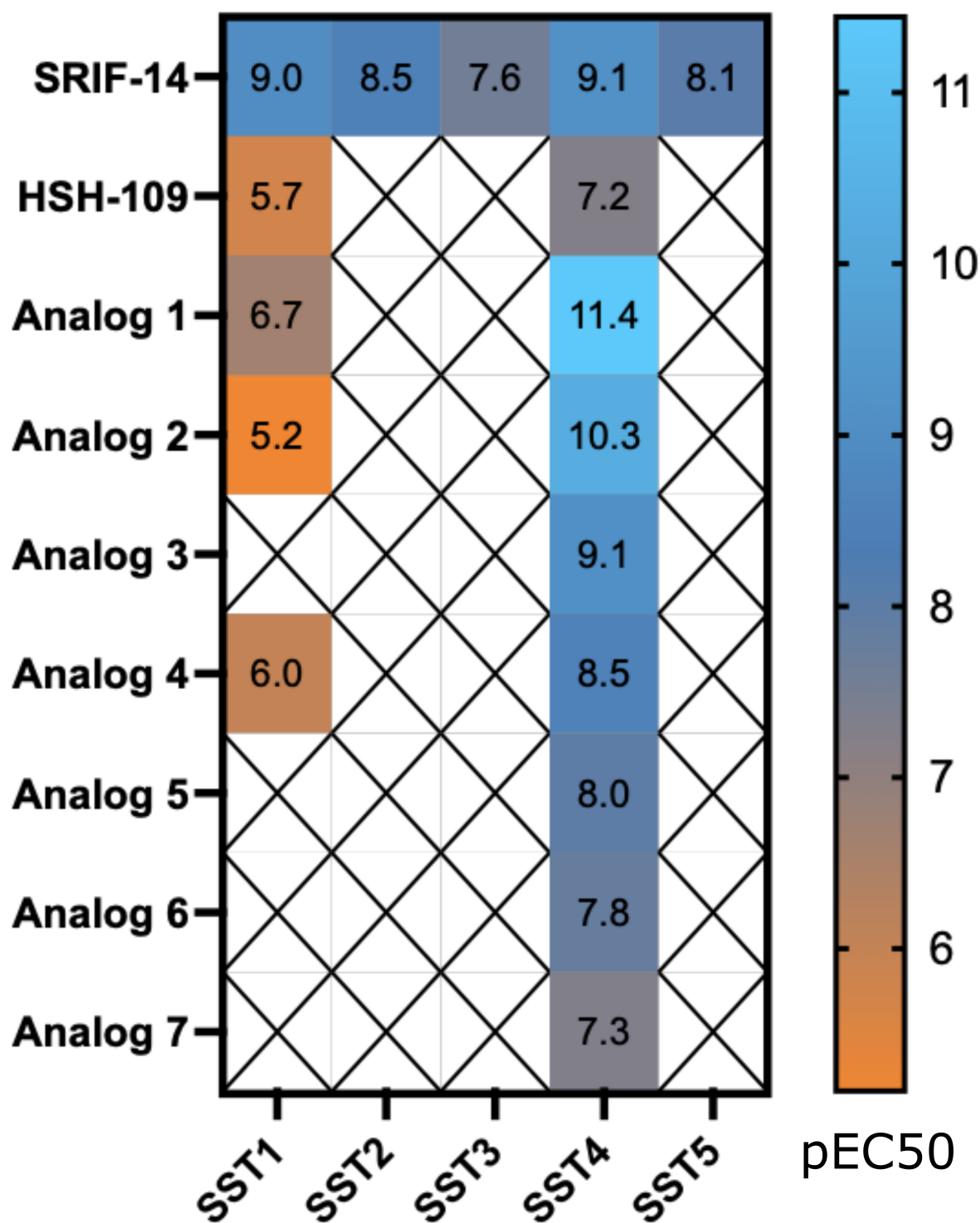
UCPH: The University of Copenhagen

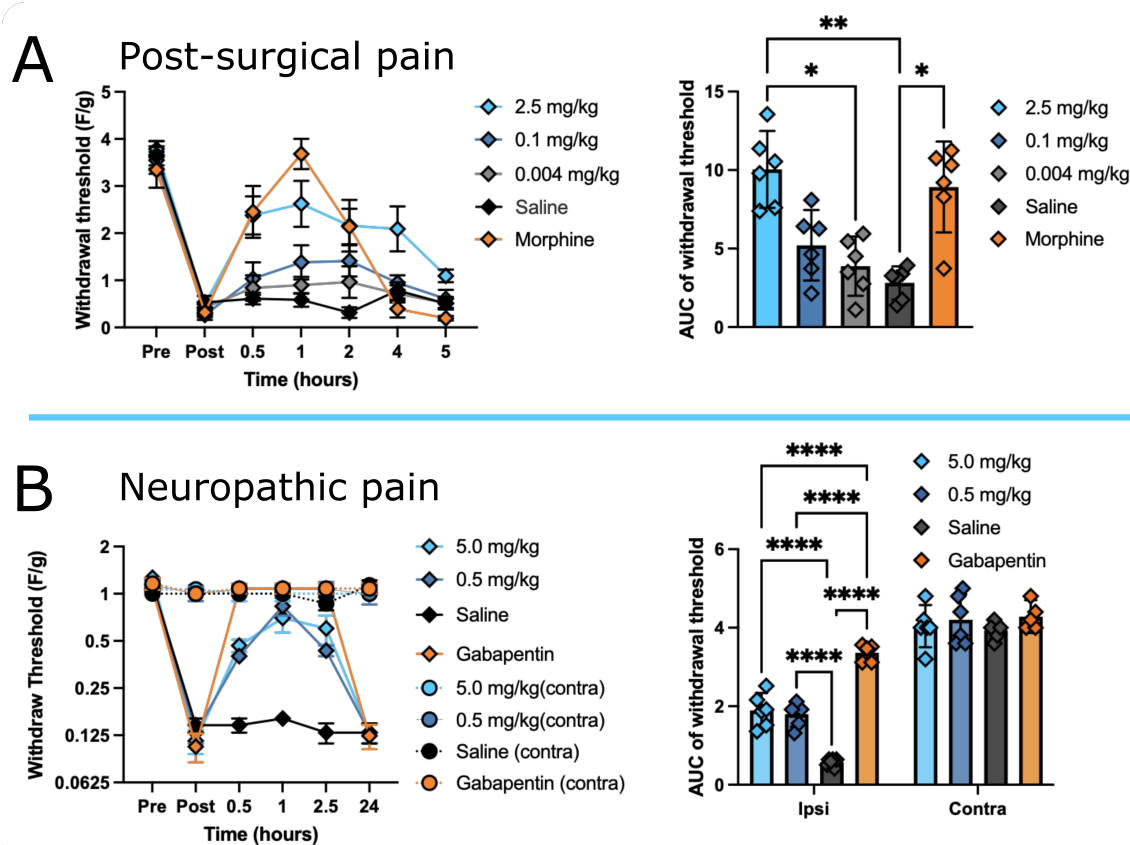
Uploads

Mechanism of action



In vitro potency





Literature references

1. Allouche, S., et al., *Front Pharmacol* **2014**, 5, 280.
2. Tauben, D., *Phys Med Rehabil Clin N Am* **2015**, 26 (2), 219-48.
3. Üçok, A., et al., *World psychiatry* **2008**, 7 (1), 58.
4. Seidel, S., et al., *Cochrane Database Syst Rev* **2013**, (8), Cd004844.
5. De La Cruz, A., *US Pharm* **2020**, 45 (3), 15-19.
6. hhs.gov - Opioid Crisis Statistics. <https://www.hhs.gov/opioids/about-the-epidemic/opioid-crisis-statistics/index.html> (accessed 2022-09-12).
7. Møller, L. N., et al., *Biochimica et Biophysica Acta (BBA)-Biomembranes* **2003**, 1616 (1), 1-84.
8. Carlton, S. M., et al., *Pain* **2004**, 110 (3), 616-627.
9. Gorham, L., et al., *Neuroscience Letters* **2014**, 573, 35-39.
10. Szolcsanyi, J., et al., *Current topics in medicinal chemistry* **2011**, 11 (17), 2253-2263.
11. Rai, U., et al., *Pharmacology & Therapeutics* **2015**, 152, 98-110.
12. Engström, M., et al., *Journal of Pharmacology and Experimental Therapeutics* **2005**, 312 (1), 332-338.
13. Kántás, B., et al., *International Journal of Molecular Sciences* **2019**, 20 (24), 6245.
14. Ramiro, I. B. L., et al., *Science Advances* **2022**, 8 (12), eabk1410.
15. Katz, M. D., et al., *Clin Pharm* **1989**, 8 (4), 255-273.
16. Zhao, W., et al., *Cell Research* **2022**, 32 (8), 761-772.
17. Mogil, J. S., *Nature Reviews Neuroscience* **2009**, 10 (4), 283-294.
18. Naik, S. R., et al., *J Postgrad Med* **2014**, 60 (3), 309-17.
19. Muley, M. M., et al., *CNS Neuroscience & Therapeutics* **2016**, 22 (2), 88-101.
20. Bjørn-Yoshimoto, W. E., et al., *Biomedicines* **2020**, 8 (8), 235.
21. DelveInsight Chronic Lower Back Pain. <https://www.delveinsight.com/infographics/chronic-lower-back-pain-clbp-market> (accessed 2022-09-13).
22. Ada Musculoskeletal Lower Back Pain. <https://ada.com/conditions/musculoskeletal-lower-back-pain/> (accessed 2022-09-14).
23. Vaughn, I. A., et al., *The Journal of Pain* **2019**, 20 (6), 629-644.
24. Colloca, L., et al., *Nature Reviews Disease Primers* **2017**, 3 (1), 17002.
25. Feldman, D. E., et al., *J Pain* **2020**, 21 (7-8), 869-880.
26. Shmigel, A., et al., *The journal of pain* **2018**, 19 (10), 1104-1112.
27. Vowles, K. E., et al., *PAIN* **2015**, 156 (4), 569-576.
28. Healthcare, G. Pain pipeline characterised by innovative programmes in early-stage development. <https://www.pharmaceutical-technology.com/comment/pain-pipeline-2019/> (accessed 2022-09-12).
29. Clexio Developing a novel non-opioid topical product to alleviate Peripheral neuropathic pain. <https://www.clexio.com/pipeline/cle-400-pain/>.

30. Lilly, E. Medicines in Development <https://www.lilly.com/discovery/clinical-development-pipeline> (accessed 2022-09-12).
31. Gloth, F. M., *Geriatrics (Basel)* **2000**, 55 (10), 46-8, 51-4.
32. Nicholson, B., et al., *Pain Med* **2004**, 5 Suppl 1, S9-s27.
33. Dahan, A., et al., *Anesthesiology* **2014**, 121 (4), 675-677.

Lay project description

Pain, especially chronic pain, is one of the most disabling and burdensome condition. Currently, the most effective drugs for pain management are the highly addictive opioids. Even though there is a growing concern over the use of these, available alternatives are not effective enough or suffer from undesirable side effects. A newly emerging target for pain therapeutics that has been gaining increasing attention in recent years is the somatostatin receptor 4. By activating this receptor, effective pain relief can be achieved, while circumventing the opioid system. We have recently identified a new compound that selectively activates this receptor and shows pain relief in several animal models. The proposed project aims to develop this compound for the future use as a non-opioid pain therapeutic.

Research Methods / Subjects

Cellular or in vitro models/systems, Animal Models, Other

Research Keywords

Biomedicine, Drug development and testing, Pharmacology

Budget

Project Overview

Requested project start date:

01/12/2023

Requested project end date:

30/11/2024

Budget

Requested project period in full years:

1

Budget summary

Year ->	1	Total
Operation	kr 950.000,00	kr 950.000,00
Administration	kr 50.000,00	kr 50.000,00
Total	kr 1.000.000,00	kr 1.000.000,00

The detailed budget is available in NORMA.

Total requested budget (DKK):

kr 1.000.000

Total project cost (DKK):

1.000.000

Supplementary information

Budget is based on quotes (Bienta, WuXi for work packages 1 and 2) or estimates (two different law firms for license consultation, as well as Plougmann Vingtoft for national phase filings).

Additional Contributions for the Project

Received from the administering institution (DKK):

0

Received from other sources (DKK):

0

Applied for from other funding sources (DKK):

0

Information for additional contributions

Appendices

To whom it may concern



2. SEPTEMBER 2022

Hosting letter for **Pioneer Innovator** application from **Walden Emil Bjørn-Yoshimoto**.

Walden Emil Bjørn-Yoshimoto is currently a postdoc but will be promoted to assistant professor starting September 15th, 2022.

The Department of Biomedical Sciences at the University of Copenhagen supports the application of **Walden Emil Bjørn-Yoshimoto** to **Novo Nordic Foundation Pioneer Innovator** with the title '**Somatostatin receptor 4 selective cone snail toxin peptides as drug leads for non-opioid pain relief**'.

The studies described in the application will be conducted at the Department of Biomedical Sciences. The Department will provide the necessary administrative support to the project, as well as adequate laboratory space and infrastructure required for the successful completion of the project, including use of existing equipment within the organisation, shared facilities and expertise.

Thus, I enthusiastically give **Walden Emil Bjørn-Yoshimoto** my full support on this project and I strongly encourage the Foundation to grant the financial necessities for its completion.

Yours sincerely,
Head of Department
Cathrine Ørskov

A handwritten signature in blue ink, appearing to read 'Cathrine Ørskov', written over a horizontal line.

Signature

Applicant Details - Walden Bjørn-Yoshimoto
Pioneer Innovator Grant 2-2022 (#0079350)

Applicant Details Type: Applicant

Pioneer Innovator Grant 2-2022 (#0079350) ~ Walden Bjørn-Yoshimoto

Personal Details

Full Name: Walden Bjørn-Yoshimoto

Email: waldenb@gmail.com

Gender: Male

Nationality: Danish

Date of Birth: 1983-06-27

Country of Residence: Denmark

Phone: 24494408

ORCID: 0000-0003-1019-9239

Most Recent Degree: Ph.D.

Date of Degree: 15/08/2017

Current Institution

Institution: Københavns Universitet

Phone Number: 35327428

Department: Department of Biomedical
Sciences

City: Copenhagen
N

Position: Assistant Professor

Country: Denmark

CV

Work and education

- 2022 → **Assistant Professor** at the University of Copenhagen, Department Biomedical Sciences.
As of September 15th, I am the daily leader of a group under Dr. Helena Safavi-Hemami, who has moved to the University of Utah. We focus on conotoxin research, with the majority of projects relating to conotoxins mimicking endogenous signaling peptides in humans.
- 2020 → **Freelance Consultant** and Founder of Walden Consulting.
Consulting, mainly on preclinical pharmacology, and occasionally writing code for unrelated subjects.
- 2019 – 2022: **Postdoc** at the University of Copenhagen, Departments of Biology and Biomedical Sciences.
My work has focused on conotoxins and GPCRs, using bioinformatics and programming approaches to finding relevant conotoxin sequences, as well as pharmacological GPCR assays to characterize them in vitro. Here, I was the daily/practical supervisor of one PhD student and two postdocs.
- 2017 – 2018: **Postdoc** at the University of Copenhagen, Department of Drug Design and Pharmacology.
My work focused on the 5-HT_{2A} receptor, where I have developed assays for assessing the proposed signaling bias of agonists at this receptor, as well as supervising a PhD student.
- 2013 – 2017: **PhD Student** at the University of Copenhagen, Department of Drug Design and Pharmacology.
I worked on the molecular pharmacology of excitatory amino acid transporters (EAAT)s. I focused on identifying novel tool compounds and investigating the molecular mechanism of transport. During a stay at NIMH/NIH, I worked on more cell biological aspects of EAATs, including intracellular trafficking.
- 2016 – 2017: **Research assistant** at the University of Copenhagen, Department of Drug Design and Pharmacology.
I had a brief leave from my PhD to do a project on the polypharmacology of the 5-HT_{2C} receptor.
- 2011 – 2013: **Research scientist** (2012-2013) and research assistant (2011) at Evolva S/A
I established their cell lab and developed assays for pharmaceutical projects focused on “diabetes”, cancer, as well as various rare diseases. I managed a technician and a part-time student helper.
- 2004 – 2010: **BSc and MSc in Biochemistry** from the University of Copenhagen.
I worked on molecular and cellular neuropharmacology in the laboratory of Professor Ulrik Gether.

Scientific output

- 16 Peer reviewed articles, 1 as corresponding author. ORCID: 0000-0003-1019-9239.
- 1 Patent awarded, 1 pending (priority patent filed).
- Reviewer: Since 2021 I have routinely reviewed articles for several journals, incl. Basic & Clinical Pharmacology & Toxicology, Marine Drugs, Toxins.
- Outreach: I have participated in various outreach activities and programs, including presentations for schools from 2. grade through “3. g” at gymnasium, activities for “Kulturnatten” (Copenhagen Culture Night), as well as writing popular science articles for “videnskab.dk”.

Scientific visits:

2015: Laboratory of Molecular and Cellular Neurobiology in the Section on Molecular and Cellular Signaling at **NIMH/NIH**, Bethesda, MD, USA. This is the laboratory of **Dr. Susan Amara**.

2014: ICCB-Longwood (Harvard Medical School) / Boston Children's Hospital, **Harvard Medical School**, Boston, MA, USA. This was done primarily in the laboratory of **Professor Clifford Woolf**.

Teaching Experience:

Since 2016 I have supervised 3 students and 2 postdocs. Officially one pharmacy student and one PhD student, and unofficially, one PhD student and two postdocs.

Since 2013 I have taught various courses both lectures, classroom teaching, and lab exercises, to pharmacy- medicine-, and odontology students. They have ranged from bachelors' courses to PhD courses and have included four different pharmacology courses, one medicinal chemistry course, and one biochemistry course.

Grants Awarded:

2015: Augustinus Foundation travel award for a research stay in Dr. Susan Amara's lab at NIMH/NIH, Bethesda, MD, USA.

2015: International Society for Neurochemistry (ISN) travel award to present at the ISN conference in Cairns, QLD, Australia.

1. I. B. L. Ramiro *et al.*, Somatostatin venom analogs evolved by fish-hunting cone snails: From prey capture behavior to identifying drug leads. *Science Advances* **8**, eabk1410 (2022).
2. C. B. M. Poulie *et al.*, (S)-2-Mercaptohistidine: A First Selective Orthosteric GluK3 Antagonist. *ACS Chemical Neuroscience*, (2022).
3. T. L. Koch *et al.*, Reconstructing the Origins of the Somatostatin and Allatostatin-C Signaling Systems Using the Accelerated Evolution of Biodiverse Cone Snail Toxins. *Molecular Biology and Evolution* **39**, msac075 (2022).
4. W. E. Bjørn-Yoshimoto *et al.*, Curses or cures: A review of the numerous benefits versus the biosecurity concerns of conotoxin research. *Biomedicines* **8**, 235 (2020).
5. P. Wu, W. E. Bjørn-Yoshimoto, M. Staudt, A. A. Jensen, L. Bunch, Identification and Structure– Activity Relationship Study of Imidazo [1, 2-a] pyridine-3-amines as First Selective Inhibitors of Excitatory Amino Acid Transporter Subtype 3 (EAAT3). *ACS chemical neuroscience* **10**, 4414-4429 (2019).
6. C. B. M. Poulie *et al.*, Design and Synthesis of 2,3-trans-Proline Analogues as Ligands for Ionotropic Glutamate Receptors and Excitatory Amino Acid Transporters. *ACS Chemical Neuroscience* **10**, 2989-3007 (2019).
7. Y. Peng *et al.*, 5-HT_{2C} receptor structures reveal the structural basis of GPCR polypharmacology. *Cell* **172**, 719-730. e714 (2018).
8. T. H. Huynh *et al.*, New 4-functionalized glutamate analogues are selective agonists at metabotropic glutamate receptor subtype 2 or selective agonists at metabotropic glutamate receptor group III. *Journal of medicinal chemistry* **59**, 914-924 (2016).
9. J. C. Hansen *et al.*, β -Sulfonamido functionalized aspartate analogues as excitatory amino acid transporter inhibitors: distinct subtype selectivity profiles arising from subtle structural differences. *Journal of medicinal chemistry* **59**, 8771-8786 (2016).
10. W. E. Bjørn-Yoshimoto, S. M. Underhill, The importance of the excitatory amino acid transporter 3 (EAAT3). *Neurochemistry international* **98**, 4-18 (2016).

Summary of own research

My background is in molecular pharmacology of neuronal targets, primarily neurotransmitter transporters, though recently I have moved towards GPCR targets. My current work focuses on cone snail toxins (conotoxins), a complex mixture of extremely diverse peptide toxins. I am pursuing two general avenues of research within conotoxins. 1) Conotoxins that mimic endogenous signaling peptides, and I have recently started efforts in 2) de novo discovery of new classes using state-of-the-art computational advances.

My most recent work on the conotoxin mimics (called "doppelganger toxins") have included the discovery of the first somatostatin receptor (SST) agonists in cone snail venom. This group of peptides was remarkably similar to the somatostatin drug analogs, such as octreotide. They included a shortened loop between cysteines forming a disulfide loop (4 amino acids, compared to 10 amino acids in somatostatin), and a D-tryptophan in a key binding position. Further, the conotoxin was very stable in plasma, as octreotide, but very unlike somatostatin. This discovery helped us to unravel the evolutionary history of somatostatin, and we showed that this hormone existed in numerous phyla, where it was previously thought to only exist in vertebrates.

Past efforts in elucidating conotoxin targets have either focused sequential sub-fractioning of venom and screening in vivo, where ion channel modulators have generally been easier to detect (hence, >95% of known conotoxins are ion channel modulators, though <1% of all have been characterized), or, frankly, chance and luck, as exemplified by α -adrenoceptor, or norepinephrine transporter modulators. I have recently discovered that subtle optimizations to the novel AI protein structure prediction tool, AlphaFold2, can enable it to predict conotoxin-receptor interactions with unprecedented accuracy. Past methods are simply not scalable (e.g., the amounts of venom needed are unobtainable for many cone snail species).

Supplementary information

I am listed as assistant professor in the above. Currently, and at the time of application deadline, I am a postdoc: However, I have been promoted starting on September 15th, the day after application deadline, and will thus be an assistant professor before start of the proposed project.

Application History

Call Name	Application Ref	Project Title	Main Applicant	Granted Amt	Status	Relevance
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